(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 691 128 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
10.01.1996 Bulletin 1996/02

(21) Application number: **95201475.1**

(22) Date of filing: **06.06.1995**

(51) Int. Cl.[6]: **A61K 31/415**, A61K 31/47, A61K 31/505, C07D 231/44, C07D 231/38, C07D 231/52, C07D 401/06, C07D 405/06, C07D 231/18, C07D 403/10, C07D 409/10, C07D 487/04, C07D 207/34

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **15.06.1994 US 259835**

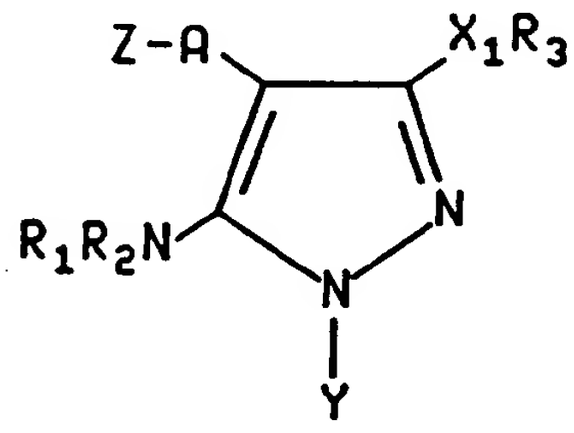
(71) Applicant: **PFIZER INC.**
New York, N.Y. 10017 (US)

(72) Inventors:
- **Bright, Gene M.**
  Groton, Connecticut 06340 (US)
- **Chen, Yuhpyng L.**
  Waterford, Connecticut 06385 (US)
- **Welch, Willard M., Jr.**
  Mystic, Connecticut 06355 (US)

(74) Representative: **Moore, James William, Dr.**
Sandwich Kent CT13 9NJ (GB)

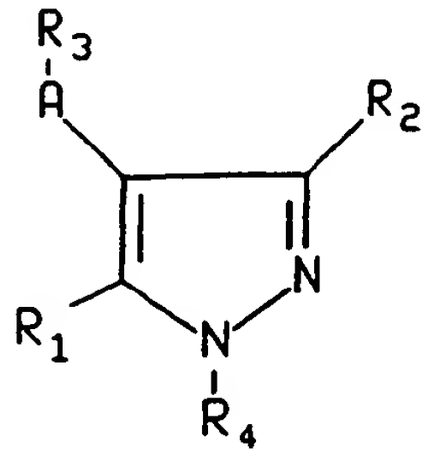
(54) Methods of administering CRF antagonists

(57) Substituted pyrrazoles of the formula



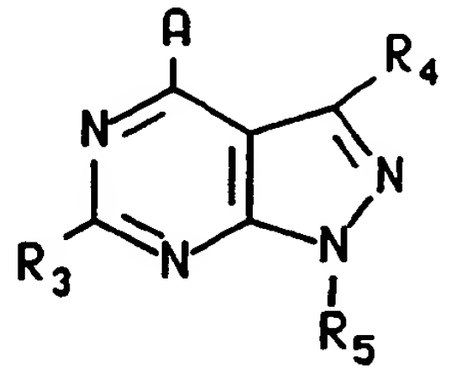
I

pyrazoles and pyzazolopyrimidines of the formula



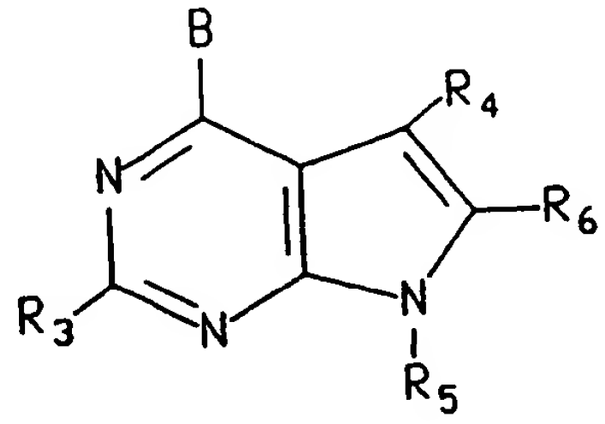
VII

compounds of the formula



VIII

and pyrrolopyzimidines of the formula



IX

hav corticotropin-releasing factor antag nist activity and as such ar of use in th treatment of a variety of stress-related disorders.

EP 0 691 128 A1

Description

Background of the Invention

The present invention relates to the treatment of certain illnesses by administering novel corticortropin-releasing factor (CRF) antagonists.

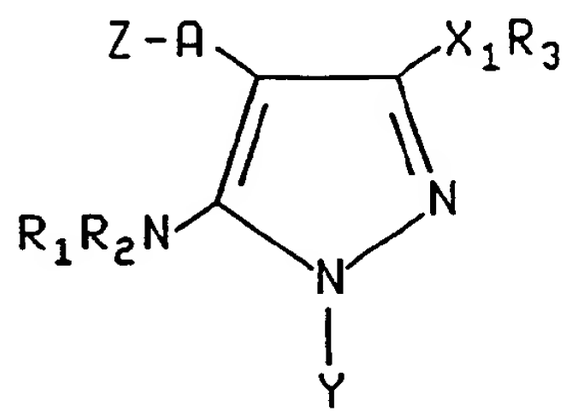
CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g. as discussed in U.S. Patent 5,063,245. A recent outline of the different activities possessed by CRF antagonists is found in M.J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991).

The CRF antagonists administered according to the invention are described in copending patent application Serial Numbers PCT/US 93/10716, PCT/US93/01539, PCT/US93/11333, and PCT/US93/10715 (Docket Nos. 8224A, 8225A, 8226A and 8308A, respectively), all of which are incorporated herein by reference.

Summary of the Invention

The present invention relates to the treatment of certain illnesses which comprises administering to a subject in need of such treatment an effective amount of a compound of the formula

(A)



I

and the pharmaceutically acceptable acid addition salts thereof,

wherein A is CH_2;

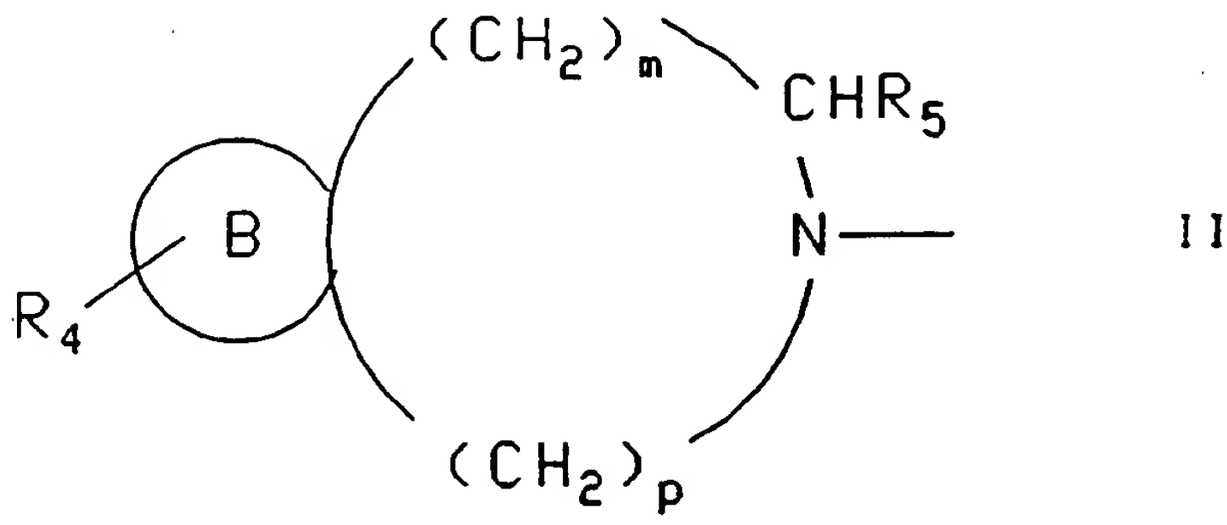
R_1, R_2 and R_3 are each independently linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl wherein the double bond is not adjacent to the N or X_1 when X_1 is oxygen or sulfur, or C_3-C_7 cycloalkyl $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4; or R_1 and R_2 when taken together with the nitrogen form a saturated four, five or six membered ring optionally condensed with benzo; and R_3 may also be $(CH_2)_qQ_1R_{19}$ wherein q is 0, 1 or 2, Q_1 is O, S, NH, N(C_1-C_6 alkyl) or a covalent bond when X_1 is not a covalent bond, and R_{19} is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl $(CH_2)_n$ wherein n is 1 to 4;

X_1 is a covalent bond, CH_2, NR wherein R is hydrogen or linear C_1-C_6 alkyl, O, or S;

Y is phenyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or piperidinyl, each of which may be substituted by one to three of any one of fluoro, chloro, bromo, or methyl, or one of trifluoromethyl; with the proviso that Y is not unsubstituted phenyl; and

Z is

(a)

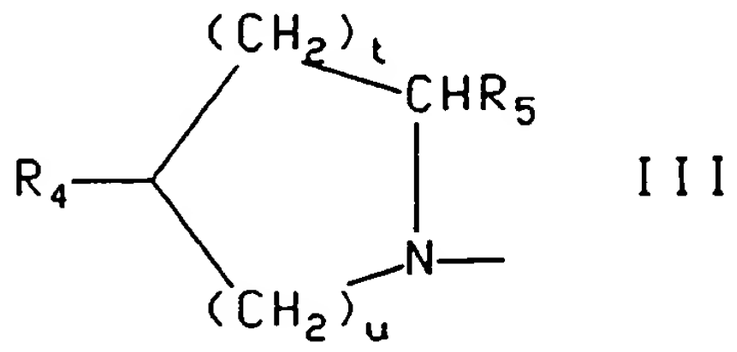


II

wherein the B ring is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazilyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thienyl, or indolyl, each of which may be substituted by methyl, methoxy, fluoro, chloro, bromo or iodo; or a saturated 5-or 6-membered carbocyclic ring or a partially unsaturated ring having one or two double bonds;

R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy, fluoro, chloro, bromo, iodo, or trifluoromethyl;
R_5 is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, or $(CH_2)_o$-X_2-$(CH_2)_r$-Q_2-R_6;
R_6 is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, or C_3-C_8 alkenyl;
X_2 and Q_2 are each independently O, S, NH, N(C_1-C_6 alkyl), or one of X_2 and Q may be a coval nt bond;
m is 0 or 1;
o is 1 or 2;
p is 1 or 2;
r is 0, 1, or 2;

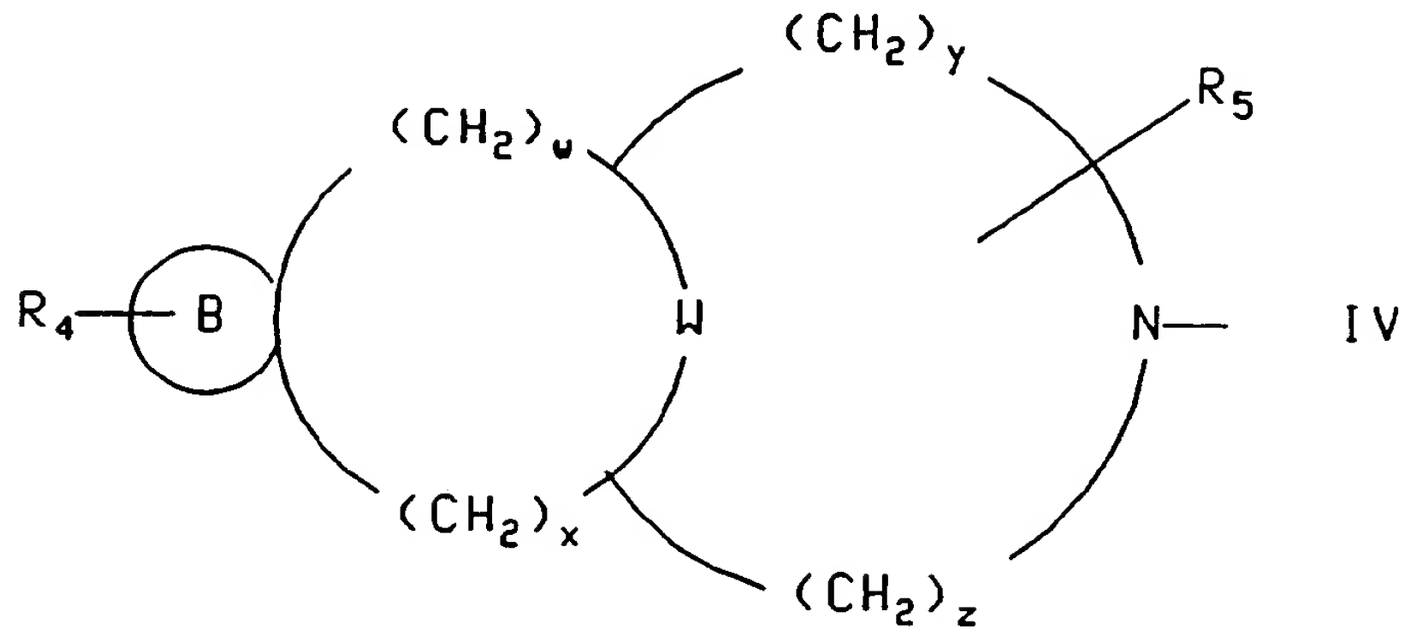
(b)



III

wherein R_4 and R_5 are as defined above, and t and u are each independently 1 or 2;
(c) -NR_7R_8 wherein R_7 and R_8 are each independently hydrogen, C_1-C_6 linear alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, $(CH_2)_vCH_2OH$, $(CH_2)_vNR_9R_{10}$, wherein v is 0 to 3, and R_9 and R_{10} are each independently hydrogen, or linear C_1-C_6 alkyl; C_1-C_{12} cycloalkyl, (C_3-C_{12} cycloalkyl) $(CH_2)_n$, (C_6-C_{10} bicycloalkyl) $(CH_2)_n$, wherein n is 0 to 4, benzofused C_3-C_6 cycloalkyl, C_1-C_6 hydroxyalkyl, phenyl, phenyl (C_1-C_3 alkylene), each of which may be substituted by one or two of hydroxy, fluoro, chloro, bromo, C_1-C_5 alkyl, or C_1-C_5 alkoxy; or R_7 and R_8 may be taken together with the nitrogen to form a saturated or partially unsaturated 5- to 7-membered ring which may contain one of O, S, NH or N(C_1-C_6 alkyl) and which may be substituted by C_1-C_6 alkyl, hydroxy or phenyl wherein any double bond(s) are not adjacent to any heteroatoms;

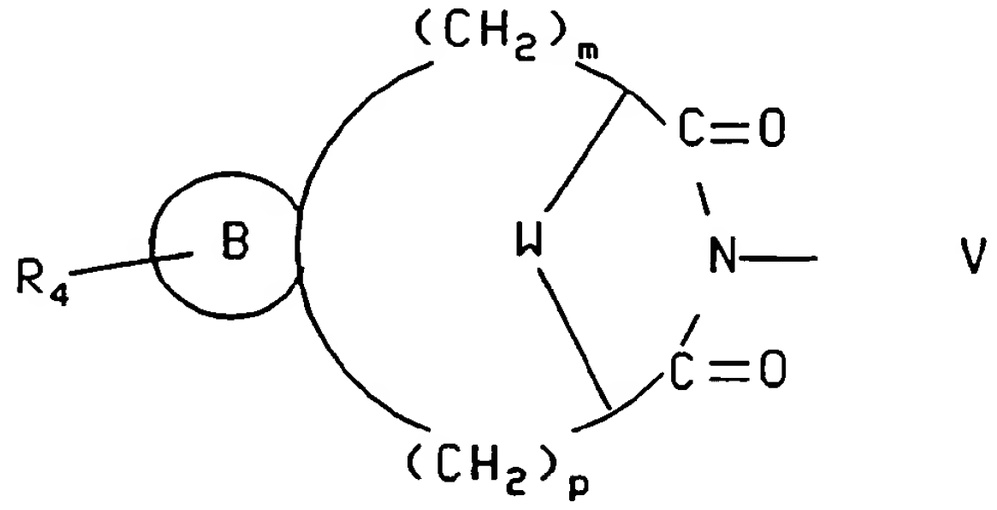
(d)



IV

wherein B, R_4 and R_5 are as defined above, w, x, y and z are each independently 1 or 2, and W is $(CH_2)_q$ wherein q is as defined above, $N(C_1\text{-}C_6$ alkyl), or oxygen;

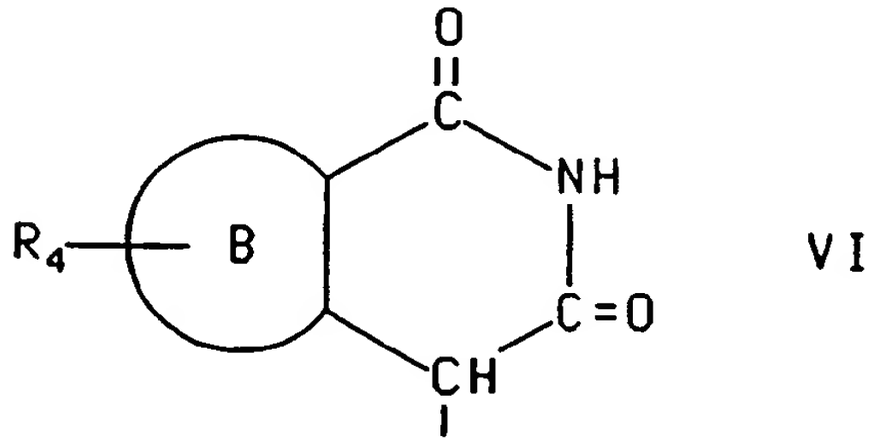
(e)



V

wherein B, R_4, m and p are as defined above;

(f)



VI

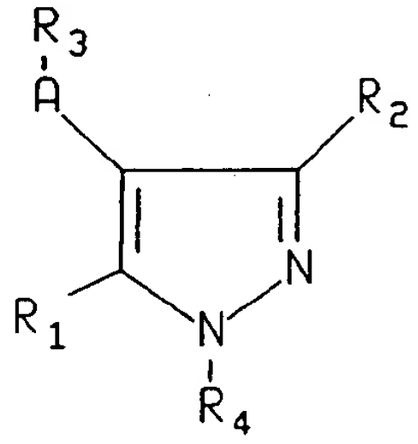
wherein B and R_4 are as defined above;

(g)

$O(CH_2)_vR_{11}$

wherein v is 0 to 3 and R_{11} is linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, or thienyl, each of which may be substituted by one or two of any one of fluoro, chloro, bromo, methyl, or trifluoromethyl;

(B)



VII

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is C=O or SO_2, or A and R_1 together with the carbons to which they are attached form pyrimidinyl or 5-pyridyl which may be substituted by R_5 which is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), SH, S(O)$_n$(C_1-C_6 alkyl) wherein n = 0, 1 or 2, wherein said C_1-C_6 alkyl may be substituted by from 1 to 3 substituents R_6 which is hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NH(C=O)CH_3, fluoro, chloro, bromo or C_1-C_3 thioalkyl;

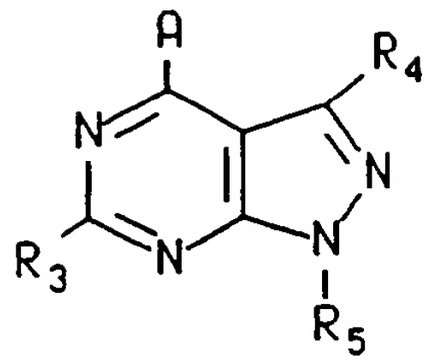
R_1 is hydrogen, C_1-C_6 alkyl, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), wher in said C_1-C_6 alkyl may be substituted by from 1 to 3 substituents R_6 as defined above;

R_2 is hydrogen, C_1-C_6 alkyl, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), SH, S(O)$_n$(C_1-C_6 alkyl) wherein n = 0, 1, or 2, cyano, hydroxy, carboxy, or amido, wherein said alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NH(C=O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (C=O)O(C_1-C_6 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_3 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 9 to 12 membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, C_1-C_6 alkyl, C_1-C_6 alkoxy, or trifluoromethyl, or one of cyano, nitro, amino, NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; and

R_4 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 3 to 8-membered cycloalkyl or 9 to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, trifluoromethyl, C_1-C_6 alkyl or C_1-C_6 alkoxy, or one of cyano, nitro, amino, NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, NH_2SO_2(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; provided that (1) R_4 is not unsubstituted phenyl; (2) when R_1 is amino, R_2 is methylthio, R_4 is 2,4,6-trichlorophenyl, and A is C=O, then R_3 is not 2-chlorophenyl; and (3) R_1 and R_2 are not both hydrogen;

(C)



VIII

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy,

O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖ ‖
O O

amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl),

NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl),
‖ ‖
O O

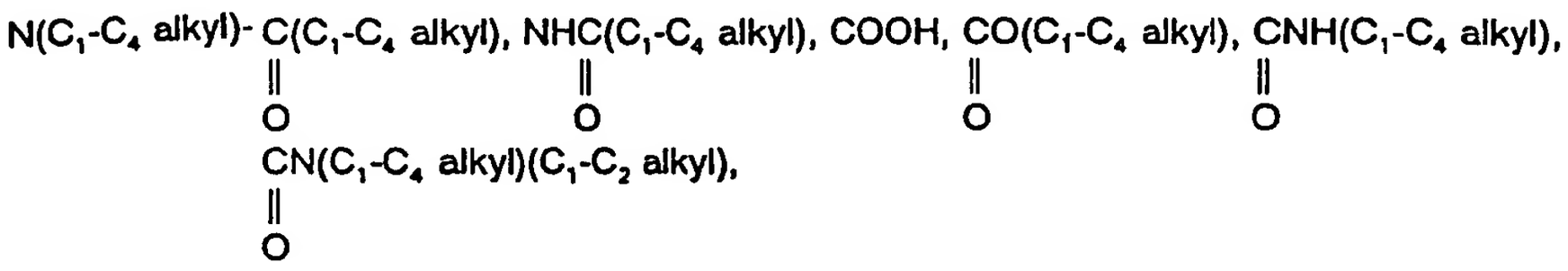
CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖ ‖
O O

SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may b substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy,

O-C -(C_1-C_6 alkyl),
‖
O

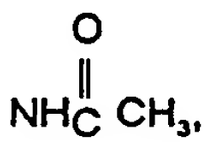
O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl),



SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

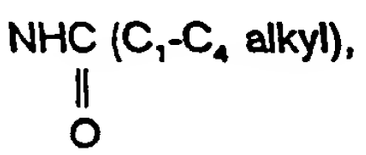
NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally containing one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_7 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino,

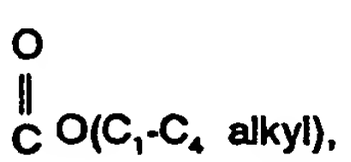


fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl) (C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido,



NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl),



C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may hav one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the pr viso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 akdyl); and

R_{12} is hydrogen or C_1-C_4 alkyl;

(a) A is not straight chain C_1-C_{12} alkyl;

EPNSDOCID: <EP 0691128A1 | >

(b) R_5 is not a sugar group;

(c) when R_3 and R_4 are hydrogen and R_5 is chloroph nyl, th n A is not NH-CH(CH_3)-(CH_2)$_3$-N(C_2H_5)$_2$;

(d) when R_3 and R_4 are hydrogen and A is NR_1R_2 wherein R_1 is C_3-C_7 cycloalkyl, and R_2 is C_2-C_6 alkenyl, phenyl-(C_1-C_6 alkyl ne) or hetero-(C_1-C_6 alkylene) wherein the hetero radical is furyl, thienyl or pyridinyl, and wherein said phenyl may be substituted by fluoro, chloro, bromo or iodo, then R_5 is not tetrahydrofuranyl or tetrahydropyranyl;

(e) when R_3 is methoxy, methylthio, or methylsulfonyl, R_4 is hydrogen, and R_5 is tetrahydrofuranyl or tetrahydropyranyl, then A is not NH(C_1-C_2alkyl), morpholinyl, hydrazino, or $NHC_2H_4C_6H_5$ which may be substituted by one methyl or two methoxy;

(f) when R_3 is hydrogen, C_1-C_6 alkyl, hydrazino, chloro, bromo, SH, or S (C_1-C_4 alkyl), R_4 is hydrogen and R_6 is C_3-C_8 cycloalkyl, then A is not hydrazino, NH(C_1-C_2 alkyl) or N(C_1-C_6 alkyl) (C_1-C_{12} alkyl);

(g) when R_3 and R_4 are hydrogen and A is NH(CH_2)$_m$ COOH wherein m is 1-12, then R_5 is not phenyl substituted by one of fluoro, chloro, bromo or iodo;

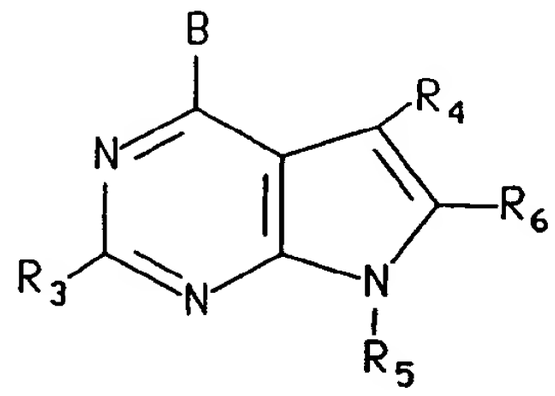
(h) when R_3 is hydrogen, hydroxy, methylthio, chloro or NHbenzyl, R_4 is hydrogen, and R_5 is chlorophenyl or bromophenyl, then A is not NH(C_1-C_{12} alkyl), NHallyl, or N(C_1-C_6 alkyl) (C_1-C_{12} alkyl), wherein said C_1-C_{12} alkyl may be substituted by NC_2H_5, or NH benzyl which may be substituted by one or two bromo, chloro, fluoro, NC_2H_5 phenyl or morpholinopropyl;

(i) when R_3 and R_4 are hydrogen and R_5 is nitrophenyl, then A is not NHR_2 wherein R_2 is C_1-C_{12} alkyl which may be substituted by two hydroxy, or R_2 is phenyl or benzyl;

(j) when R_3 is chloro or O(C_1-C_6 alkyl), R_4 is hydrogen, and A is NR_1R_2 wherein R_1 and R_2 are independently hydrogen or C_1-C_6 alkyl, then R_5 is not chlorophenyl; and

(k) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'deoxy-ribofuranosyl; or

(D)



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy,

O-C -(C_1-C_6 alkyl), O-C NH(C_1-C_4 alkyl), O-C -N(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖ ‖ ‖
O O O

alkyl)(C_1-C_2 alkyl amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl),

N(C_1-C_4alkyl)C (C_1-C_4 alkyl), NHC (C_1-C_4 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl),
‖ ‖ ‖ ‖
O O O O

C N(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖
O

SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and said $C_1\text{-}C_6$ alkyl may contain one or two double or triple bonds;

R_2 is $C_1\text{-}C_{12}$ alkyl, aryl or ($C_1\text{-}C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1\text{-}C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or $C_1\text{-}C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1\text{-}C_6$ alkoxy,

$$\text{O-C-}(C_1\text{-}C_6\text{ alkyl}),\quad \text{O-C-N}(C_1\text{-}C_4\text{ alkyl})(C_1\text{-}C_2\text{ alkyl}),$$
(each C=O)

$S(C_1\text{-}C_6$ alkyl), NH_2, $NH(C_1\text{-}C_2$ alkyl), $N(C_1\text{-}C_2$ alkyl) ($C_1\text{-}C_4$ alkyl),

$$\text{N}(C_1\text{-}C_4\text{ alkyl})\text{-C}(C_1\text{-}C_4\text{ alkyl}),\quad \text{NHC}(C_1\text{-}C_4\text{ alkyl}),$$
(each C=O)

$$\text{COOH},\quad \text{C O}(C_1\text{-}C_4\text{ alkyl}),\quad \text{C NH}(C_1\text{-}C_4\text{ alkyl}),\quad \text{C N}(C_1\text{-}C_4\text{ alkyl})(C_1\text{-}C_2\text{ alkyl}),$$
(each C=O)

SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and wherein said $C_1\text{-}C_{12}$ alkyl or $C_1\text{-}C_{10}$ alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$, may form a saturated 3- to 8-membered ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl;

R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1\text{-}C_6$ alkyl), $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SH, $S(C_1\text{-}C_4$ alkyl), $SO(C_1\text{-}C_4$ alkyl), or $SO_2(C_1\text{-}C_4$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents R_8 independently selected from the group consisting of hydroxy, $C_1\text{-}C_3$ alkoxy, fluoro, chloro or $C_1\text{-}C_3$ thioalkyl;

R_4 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_2$ alkyl), $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido,

$$\text{NHC}(C_1\text{-}C_4\text{ alkyl}),$$
(C=O)

$NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl),

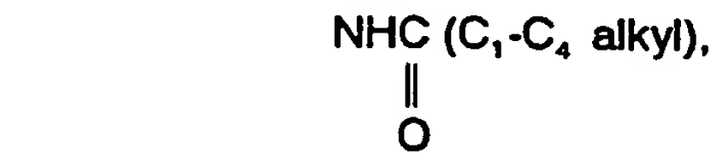
$$\text{C O}(C_1\text{-}C_4\text{ alkyl}),$$
(C=O)

$C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

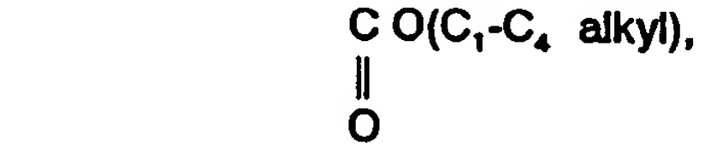
R_6 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkanoyl, phenyl or phenylmethyl, wherein

each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, NH(C_1-C_4 alkyl), N(C_1-C_4)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido,



NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl),



C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) B is not straight chain C_1-C_{12} alkyl, (2) wh n R_5 is unsubstituted cycloakyl, R_3 and R_4 are hydrogen, and R_6 is hydrogen or methyl, then B is not NHR_2 wherein R_2 is benzyl or thienylmethyl, and (3) when R_5 is p-bromophenyl, and R_3, R_4 and R_6 are methyl, then B not methylamino or hydroxyethylamino, said disorders being selected from group consisting of panic, phobias including agoraphobia, social phobia, and simple phobia, obsessive-compulsive disorder, post-traumatic stress disorder, single episode depression, recurrent depression, dysthymia, bipolar disorders, cyclothymia, mood disorders, postpartum depression, child abuse induced depression, sleep disorders, stress induced pain perception including fibromyalgia, fibromyalgic sleep disorders, rheumatoid arthritis, osteoarthritis, psoriasis, euthyroid sick syndrome, syndrome of inappropriate antidiarrhetic syndrome hormone (ADH), bulimia nervosa eating disorder, and obesity.

More specific compounds of formula I of the invention include those wherein Y is phenyl substituted by three substituents one each at positions 2, 4 and 6, e.g. 2,4,6-trichlorophenyl, 2,6-dichloro-4-trifluoromethylphenyl, or 2,6-dichloro-4-fluorophenyl. Other more specific compounds of formula I include those wherein XR_3 is ethyl or methylthio, those wherein R_1 and R_2 are each methyl, and those wherein Z is NR_7R_8 and R_7 is phenyl or phenyl substituted by one of fluoro, chloro, nitro, methyl or methoxy and R_8 is as defined above, preferably, $(CH_2)_3OH$, CH_2CH_2OH or methyl.

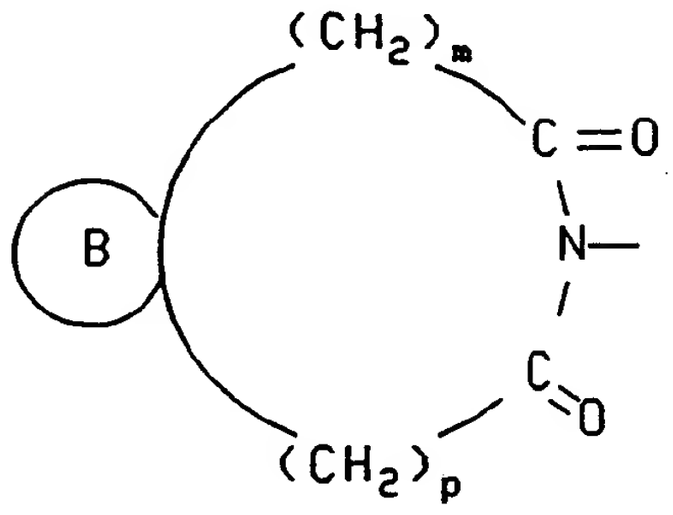
Preferred compounds of formula I are those wherein Z is 1,2,3,4-tetrahydroisoquinolin-2-yl substituted by R_5 which is -$(CH_2)_o$-X_2-$(CH_2)_r$-Q_2-R_6, more specifically R_5 is -$(CH_2)_k$OH wherein k is an integer of 1 to 4, or -$CH_2OCH_2CH_2OR_6$. Other preferred compounds of formula I are those wherein Z is 1,2,3,4-tetrahydroquinolin-2-yl wherein R_5 is substituted at position 3, and the absolute configuration at the 3 position is either S or R or R,S.

Preferred compounds of the formula I include those wherein Z is as defined in above subparagraph (h); and those wherein Z is as defined in (h), A is linked to position 1, F, G, H, I, J and K are each carbon, and R_{14} is methoxy, ethoxy, isopropoxy, or cyclopropylmethoxy at position 2.

Other preferred compounds of formula I are those wherein Z is as defined in above subparagraph (h), A is linked to position 1, K is nitrogen, F, G, H, I, and J are each carbon, and R_{14} is -X_2-$(CH_2)_r$$Q_2$$R_6$ at position 2; those wherein Z is as defined in (h), A is linked to position 1, K is nitrogen, F, G, H, I, and J are each carbon, and R_{14} is methoxy, ethoxy, isopropoxy, or cyclopropylmethoxy at position 2; and those wherein Z is as defined in (h), A is at position 1, and R_{14} is ethoxy, isopropoxy or cyclopropylmethoxy at position 2. In these preferred compounds of formula I wherein Z is as defined in (h), R_{12} and R_{13} are preferably hydrogen.

Other preferred compounds of formula I are those wherein Z is as defined in subparagraph (a), B is phenyl, p and m are each 1, and R_5 is CH_2OCH_3.

Preferred compounds of formula I include those wherein Z is



wherein B is phenyl, m is O, and p is 1.

More specific compounds of the formula VII include those wherein R_3 is phenyl substituted independently with one or two of fluoro, chloro, bromo, methyl, trifluoromethyl, nitro, C_1-C_6 alkyl, C_1-C_6 alkyloxy, SO_2NH_2, $SO_2NH(C_1$-C_6 alkyl), $SO_2N(C_1$-C_6 alkyl)$_2$, or R_3 is primary, secondary or tertiary alkyl of from 4-9 carbon atoms wherein said C_4-C_9 alkyl may contain from one to two double or triple bonds and may be substituted by from 1 to 3 substituents R_6 which is hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, $NH(C=O)CH_3$, fluoro, chloro, br m , or C_1-C_3 thioalkyl.

More specific compounds of the formula VII are those wherein A is C=O, those wherein R_1 is amino, m thylamino or dimethylamino; those wherein R_2 is ethyl or methylthio and those wherein R_4 is 2,4,6-trichlorophenyl, 2,4,6-trimethylphenyl, 2,6-dichloro-4-trifluoromethylphenyl or 4-bromo-2,6-dimethylphenyl.

More specific compounds of formula VII further include those wherein R_3 is phenyl which may be substituted at positions 2 or 5 with one or two of methyl, C_2-C_6 straight-chain or branched alkyl, trifluoromethyl, fluoro, chloro, bromo or nitro, those wherein A and R_1 together form a pyrimidine ring, such that the bicyclic structure formed is pyrazolo[3,4-d]pyrimidine, and R_5 is substituted at the 6 position; and those wherein R_3 is phenyl substituted independently with one or two of fluoro, chloro, bromo, methyl, trifluoromethyl, nitro, C_1-C_6 alkyl, C_1-C_6 alkyloxy, SO_2NH_2, $SO_2NH(C_1$-C_6 alkyl), or $SO_2N(C_1$-C_6alkyl)$_2$, R_4 is 2,4,6-trichlorophenyl, 2,4,6-trimethylphenyl, 2,6-dichloro-4-trifluoromethylphenyl or 4-bromo-2,6-dimethylphenyl, and R_2 is methylthio, methyl or ethyl.

More specific compounds of formula VII also include those wherein R_3 is phenyl substituted independently with one or two of fluoro, chloro, bromo, methyl, trifluoromethyl, nitro, C_1-C_6 alkyl, C_1-C_6 alkyloxy, SO_2NH_2, $SO_2NH(C_1$-C_6 alkyl), $SO_2N(C_1$-C_6 alkyl)$_2$, or R_3 is primary, secondary or tertiary alkyl of from 4-9 carbon atoms wherein said C_4-C_9 alkyl may contain from one to two double or triple bonds and may be substituted by from 1 to 3 substituents R_6 which is hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, $NH(C=O)CH_3$, fluoro, chloro, bromo or C_1-C_3 thioalkyl; R_4 is 2,4,6-trichlorophenyl, 2,4,6-trimethylphenyl, 2,6-dichloro-4-trifluoromethylphenyl or 4-bromo-2,6-dimethylphenyl; R_1 is amino, methylamino or dimethylamino; and R_2 is methylthio or ethyl.

More specific compounds of the formula VIII are those wherein A is NR_1R_2, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl, which may be substituted by one of hydroxy, fluoro or C_1-C_2 alkoxy, and may contain one double or triple bond, and R_2 is benzyl or C_1-C_5 alkyl which may contain one double or triple bond, wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by fluoro, C_1-C_6 alkyl, or C_1-C_6 alkoxy; and those wherein A is $CR_1R_2R_{11}$ wherein R_1 is C_1-C_6 alkyl which may be substituted by one C_1-C_6 alkoxy or hydroxy, R_2 is benzyl or C_1-C_6 alkyl wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by one C_1-C_6 alkyl, C_1-C_6 alkoxy, fluoro, chloro or bromo, and R_{11} is hydrogen or fluoro.

More specific compounds of the formula VIII include those wherein R_2 is (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

More specific compounds of the formula VIII further include those wherein R_2 is benzyl para-substituted by one of ethyl, t-butyl, methoxy, trifluoromethyl, nitro, fluoro chloro, or methyl.

Other more specific compounds of the formula VIII include those wherein R_2 is attached through a methylene or ethylene bridge to quinolyl, pyrrolyl, pyrrolidinyl, pyridyl, tetrahydropyranyl, cyclopropyl, piperidinyl, or benzyl-pip ridinyl.

More specific compounds VIII further include those wherein R_1 or R_2 is C_1-C_6 alkyl which may be substituted by one of hydroxy, methoxy, th xy, chl ro, fluoro, $OC(O)CH_3$, $OC(O)NHCH_3$, r $C(O)NH_2$.

Other more specific compounds VIII include those wherein R_2 is C_1-C_6 alkyl substituted by tw of methoxy r ethoxy, or one of $COOC_2H_5$, methylthio, or phenyl.

Other more specific compounds VIII include thos wherein A is NR_1R_2 or CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring having one more nitrogen, sulfur, and/or one oxygen, e.g. pyr-

rolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrazinyl or pyrimidyl.

Other more specific compounds VIII includes those wherein A is $NHCHR_1R_2$ or $OCHR_1R_2$ in which CHR_1R_2 is a 5- or 6-membered ring which may contain one oxygen or sulfur, e.g. tetrahydrofuranyl, tetrahydrothiafuranyl and cyclopentanyl.

Preferred compounds of the formula IX of the invention are those wherein B is NR_1R_2, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl, which may be substituted by one of hydroxy, fluoro or C_1-C_2 alkoxy, and may contain one double or triple bond; those wherein R_2 is benzyl or C_1-C_6 alkyl which may contain one double or triple bond, wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by fluoro, C_1-C_6 alkyl, or C_1-C_6 alkoxy; those wherein R_3 is methyl, ethyl, fluoro, chloro or methoxy; those wherein R_4 and R_6 are independently hydrogen, methyl, or ethyl; and those wherein R_5 is phenyl substituted by two or three substituents, said substituent being independently fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may be substituted by one of hydroxy, C_1-C_4 alkoxy or fluoro and may have one double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, or -C(O)(C_1-C_4 alkyl).

In specific methods of the invention, said compound is

2-{1-[1-(2,6-dichloro-4-tirfluoromethylphenyl)-5-dimethylamino-3-ethyl-1H-pyrazol-4-ylmethyl]-napthalen-2-yloxy}-ethanol;

enantiomeric [4-(3-methoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylaminederivedfrom(+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline;

enantiomeric [2-(2,6-dichloro-4-trifluoromethylphenyl)-4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-5-ethyl-2H-pyrazol-3-yl]-dimethylamine derived from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline;

[2-(2,6-dichloro-4-trifluoromethylphenyl)-5-ethyl-4-(7-methoxyquinolin-8-ylmethyl)-2H-pyrazol-3-yl]-dimethylamine;

[2-(2,6-dichloro-4-trifluoromethylphenyl)-4-)2-ethoxy-napthalen-1-ylmethyl)-5-ethyl-2H-pyrazol-3-yl]-dim thylamine;

[4-(2-ethoxynapthalen-1-ylmethyl)-5-ethyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine;

[4-(7-methoxyquinolin-8-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine;

2-{1-[5-dimethlamino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-napthalen-2-yloxy}-ethanol;

enantiomeric [2-(2,6-dichloro-4-trifluoromethlphenyl)-5-ethyl-4-(3-methoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-2H-pyrazol-3-yl]-dimethylamine derived from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline;

[4-(2-cyclopropylmethoxynapthalen-1-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine.

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dimethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-bis-trifluoromethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone,

[5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone, or

[5-amino-1-(4-bromo-2,6-dimethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dibromophenyl)methanone.

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dimethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-bis-trifluoromethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone,

[5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone, or

[5-amino-1-(4-bromo-2,6-dimethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dibromophenyl)methanone;

3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopr pylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine.
n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethylpropyl)amine; or
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

Detailed Description of the Invention

Whenever reference herein is made to groups $(CH_2)_qQ_1R_{19}$ and $(CH_2)_0$-X_2-$CH_2)_r$-Q_2-R_6, then X_1 and Q_1, and X_2 and Q_2, respectively, are not both a heteroatom when q or r, respectively, is 1.

Whenever one of the substituents, e.g. Y or R_1 in formula I, is a heterocyclic group, the attachment of the group is through a carbon atom.

Whenever reference is made herein to alkyl, a straight and branched chain alkyl of one to six carbon atoms is included, such as methyl, ethyl, isopropyl or hexyl.

Whenever reference is made herein to C_1-C_6 alkyl, in the definition of R_5 and R_1 formula VII, this includes unsaturated C_2-C_6 alkyl, such as C_2-C_6 alkyl having one double or triple bond, C_3-C_6 alkyl having two double bonds, and C_4-C_6 alkyl having two triple bonds.

Whenever reference is made herein to 3- to 8-membered cycloalkyl or 9-to 12-membered bicycloalkyl containing one to three of O, S or N-Z, it is understood that the oxygen and sulfur ring atoms are not adjacent to each oth r. The three membered cycloalkyl has just one O, S or N-Z. An example of a six membered cycloalkyl having O and N is morpholinyl.

Whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which "may contain one or two double r triple bonds" in the definitions of R_1, R_2 and R_3, it is understood that at least two carbons are present in the alkyl for one double or triple bond, and at least four carbons for two double and triple bonds.

Whenever an alkoxy group, e.g. in the definitions of R_1 and R_2 in formula VIII, may have a double or triple bond, it is understood that such double or triple bond is not directly attached to the oxygen.

The compounds of formulae I, VII, VIII and IX, their pharmaceutically acceptable salts, and their preparation are described in, respectively, patent applications PCT/US93/10716, PCT/US93/10539, PCT/US93/11333, and PCT/US93/10715. The compounds of formulae I, VII, VIII and IX, and their pharmaceutically acceptable salts are designated hereafter as "the active compound". It is noted that the active compounds are described above substantially in accordance with the respective patent applications.

The acid addition salts are prepared in a conventional manner by treating a solution or suspension of the free base of the active compound with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the active compounds and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tabl ts, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsul s. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential activ ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or

dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of th active compound in sesam or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and th liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

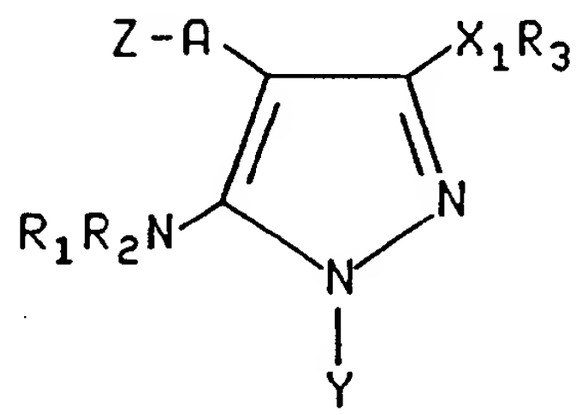
The effective dosage for the active compound depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. The daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. The daily dosage may be given in a single dose or up to three divided doses.

The methods for testing the active compounds for their CRF antagonist activity are as described in Endocrinology, 116, 1653-1659 (1985) and Peptides 10, 179-188 (1989) which determine the binding affinity of a test compound for a CRF receptor. The binding affinities for the active compounds, expressed as IC_{50} values, generally range from about 0.2 namomolar to about 10 micromolar.

Claims

1. The use of a compound of the formula

(A)



I

or a pharmaceutically acceptable acid addition salts thereof,
wherein A is CH_2;

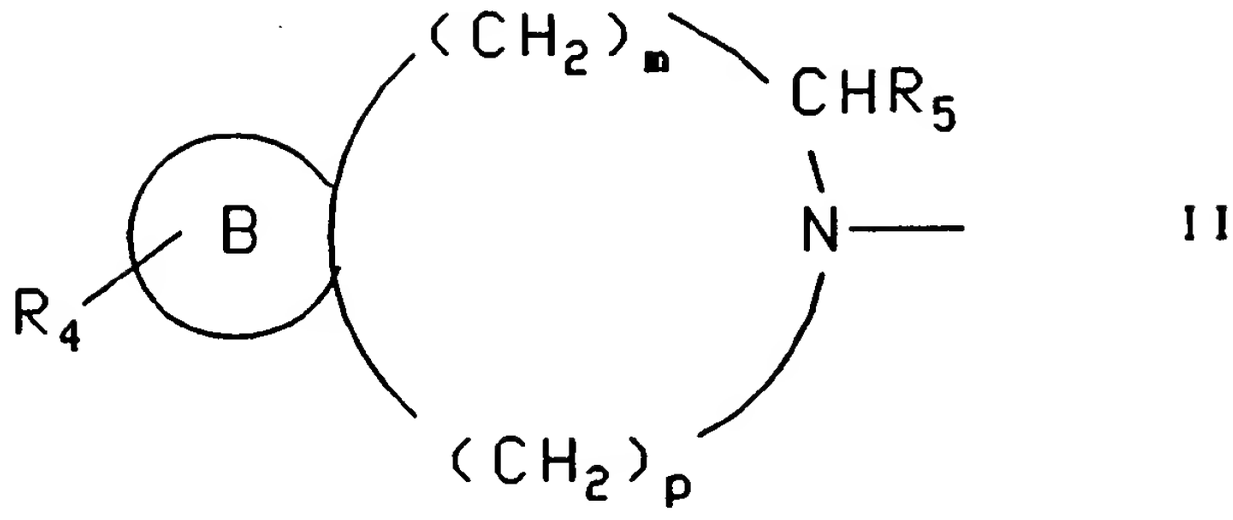
R_1, R_2 and R_3 are each independently linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl wherein the double bond is not adjacent to the N or X_1 when X_1 is oxygen or sulfur, or C_3-C_7 cycloalkyl $(CH_2)_n$ wherein n is 0, 1, 2, 3 or 4; or R_1 and R_2 when taken together with the nitrogen form a saturated four, five or six membered ring optionally condensed with benzo; and R_3 may also be $(CH_2)_qQ_1R_{19}$ wherein q is 0, 1 or 2, Q_1 is O, S, NH, N(C_1-C_6 alkyl) or a covalent bond when X_1 is not a covalent bond, and R_{19} is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, C_3-C_8 cycloalkyl or C_3-C_6 cycloalkyl $(CH_2)_n$ wherein n is 1 to 4;

X_1 is a covalent bond, CH_2, NR wherein R is hydrogen or linear C_1-C_6 alkyl, O, or S;

Y is phenyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, or piperidinyl, each of which may be substituted by one to three of any one of fluoro, chloro, bromo, or methyl, or one of trifluoromethyl; with the proviso that Y is not unsubstituted phenyl; and

Z is

(a)



II

wherein the B ring is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazilyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thienyl, or indolyl, each of which may be substituted by methyl, methoxy, fluoro, chloro, bromo or iodo; or a saturated 5-or 6-membered carbocyclic ring or a partially unsaturated ring having one or two double bonds;

R_4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy, fluoro, chloro, bromo, iodo, or trifluoromethyl;

R_5 is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, or $(CH_2)_o$-X_2-$(CH_2)_r$-Q_2-R_6;

R_6 is hydrogen, linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, or C_3-C_8 alkenyl;

X_2 and Q_2 are each independently O, S, NH, N(C_1-C_6 alkyl), or one of X_2 and Q may be a covalent bond;

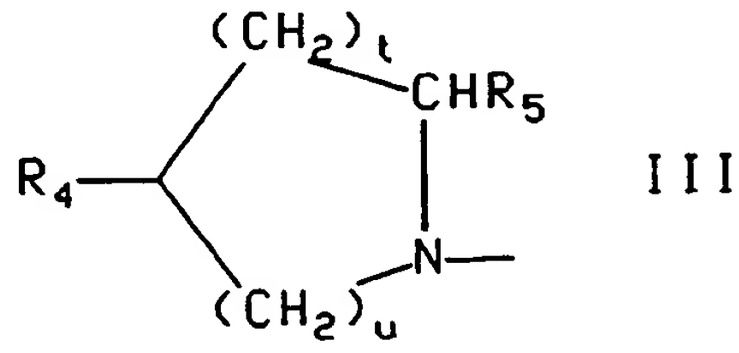
m is 0 or 1;

o is 1 or 2;

p is 1 or 2;

r is 0, 1, or 2;

(b)

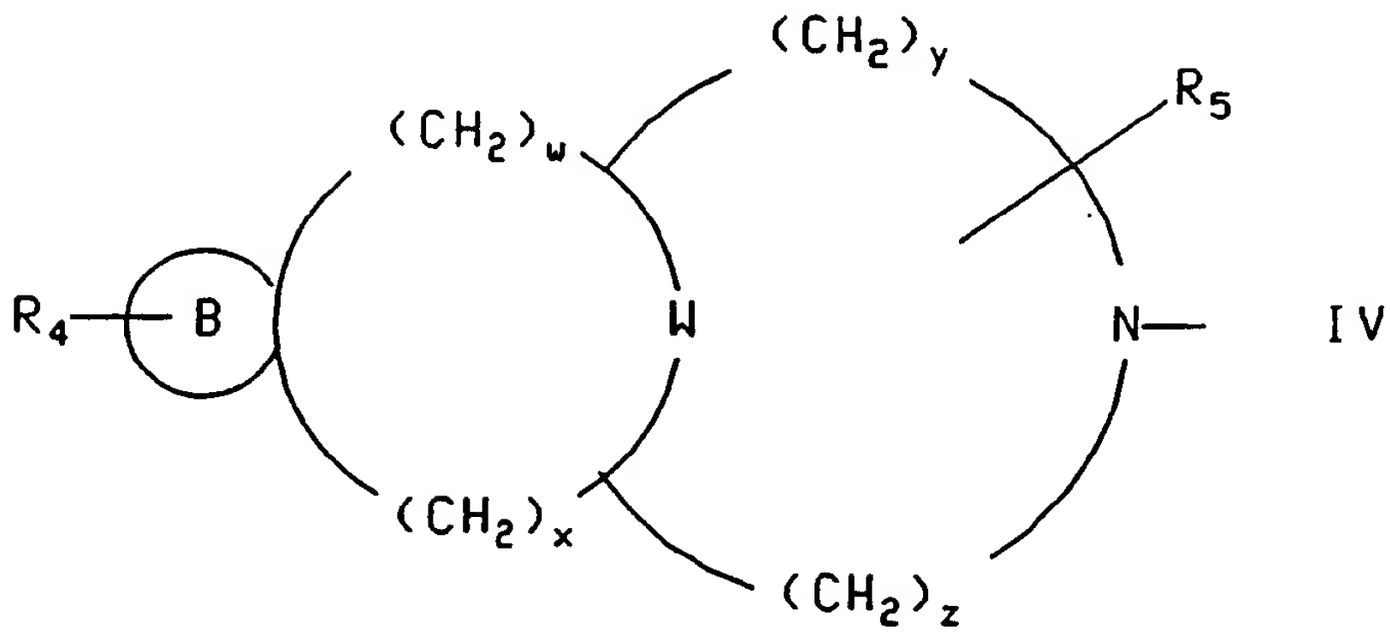


III

wherein R_4 and R_5 are as defined above, and t and u are each independently 1 or 2;

(c) -NR_7R_8 wherein R_7 and R_8 are each independently hydrogen, C_1-C_6 linear alkyl, branched C_3-C_8 alkyl, C_3-C_8 alkenyl, $(CH_2)_vCH_2OH$, $(CH_2)_vNR_9R_{10}$, wherein v is 0 to 3, and R_9 and R_{10} are each independently hydrogen, or linear C_1-C_6 alkyl; C_1-C_{12} cycloalkyl, (C_3-C_{12} cycloalkyl) $(CH_2)_n$, (C_6-C_{10} bicycloalkyl) $(CH_2)_n$, wherein n is 0 to 4, benzofused C_3-C_6 cycloalkyl, C_1-C_6 hydroxyalkyl, phenyl, phenyl (C_1-C_3 alkylene), each of which may be substituted by one or two of hydroxy, fluoro, chloro, bromo, C_1-C_5 alkyl, or C_1-C_5 alkoxy; or R_7 and R_8 may be taken together with the nitrogen to form a saturated or partially unsaturated 5- to 7-membered ring which may contain one of O, S, NH or N(C_1-C_6 alkyl) and which may be substituted by C_1-C_6 alkyl, hydroxy or phenyl wherein any double bond(s) are not adjacent to any heteroatoms;

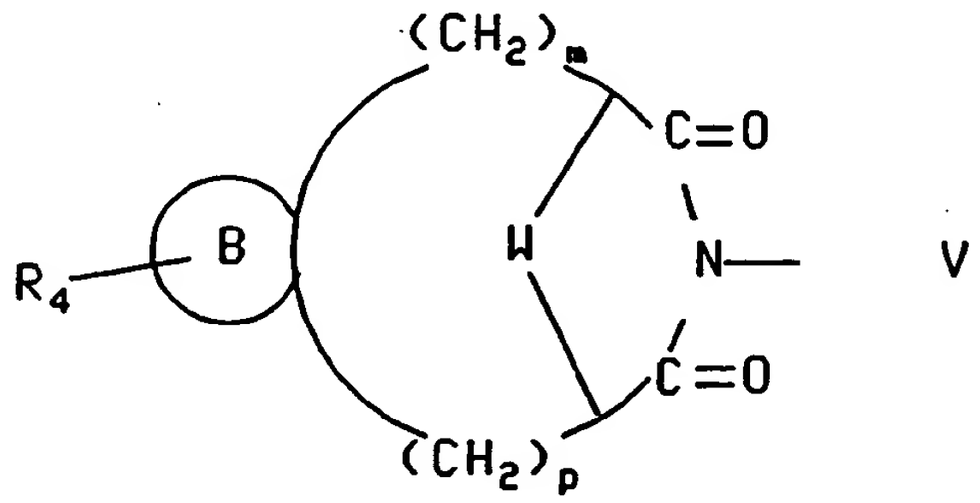
(d)



IV

wherein B, R_4 and R_5 are as defined above, w, x, y and z are each independently 1 or 2, and W is $(CH_2)_q$ wherein q is as defined above, $N(C_1\text{-}C_6$ alkyl), or oxygen;

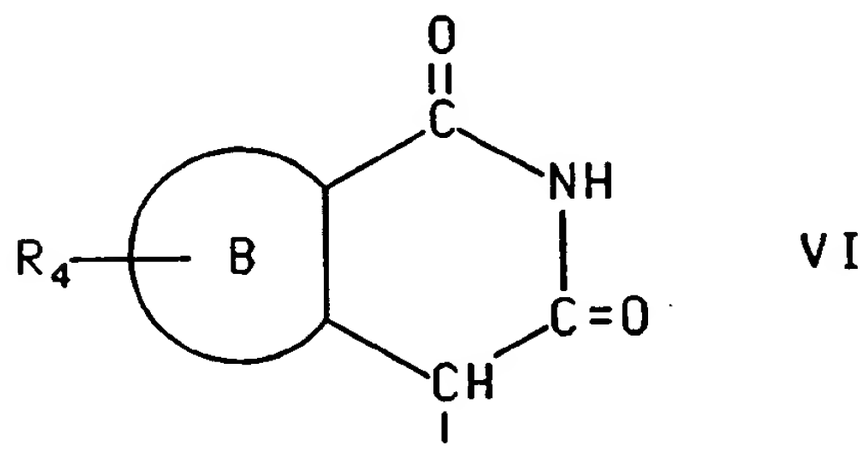
(e)



V

wherein B, R_4, m and p are as defined above;

(f)



VI

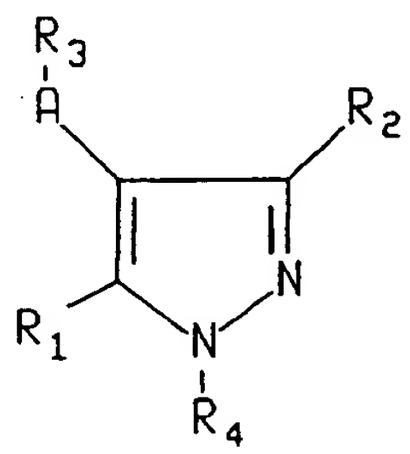
wherein B and R_4 are as defined above;

(g)

$O(CH_2)_vR_{11}$

wherein v is 0 to 3 and R_{11} is linear C_1-C_6 alkyl, branched C_3-C_8 alkyl, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, benzimidazolyl, furanyl, benzofuranyl, thiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, isoxazolyl, benzisoxazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, benzoxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, or thienyl, each of which may be substituted by one or two of any one of fluoro, chloro, bromo, methyl, or trifluoromethyl;

(B)



VII

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is C=O or SO_2, or A and R_1 together with the carbons to which they are attached form pyrimidinyl or 5-pyridyl which may be substituted by R_5 which is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), SH, S(O)$_n$(C_1-C_6 alkyl) wherein n = 0, 1 or 2, wherein said C_1-C_6 alkyl may be substituted by from 1 to 3 substituents R_6 which is hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NH(C=O)CH_3, fluoro, chloro, bromo r C_1-C_3 thioalkyl;

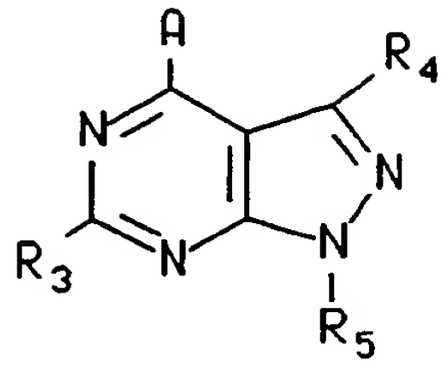
R_1 is hydrogen, C_1-C_6 alkyl, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), wherein said C_1-C_6 alkyl may be substituted by from 1 to 3 substituents R_6 as defined above;

R_2 is hydrogen, C_1-C_6 alkyl, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), SH, S(O)$_n$(C_1_C_6 alkyl) wherein n = 0, 1, or 2, cyano, hydroxy, carboxy, or amido, wherein said alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NH(C=O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (C=O)O(C_1-C_6 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_3 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 9 to 12 membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, C_1-C_6 alkyl, C_1-C_6 alkoxy, or trifluoromethyl, or one of cyano, nitro, amino, NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, NHSO_2(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; and

R_4 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 3 to 8-membered cycloakyl or 9 to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, trifluoromethyl, C_1-C_6 alkyl or C_1-C_6 alkoxy, or one of cyano, nitro, amino, NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, NH_2SO_2(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or ac tyl; provided that (1) R_4 is not unsubstituted phenyl; (2) when R_1 is amino, R_2 is methylthio, R_4 is 2,4,6-trichlorophenyl, and A is C=O, then R_3 is not 2-chlorophenyl; and (3) R_1 and R_2 are not both hydrogen;

(C)



VIII

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy,

O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖ ‖
O O

amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl),

NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl),
‖ ‖
O O

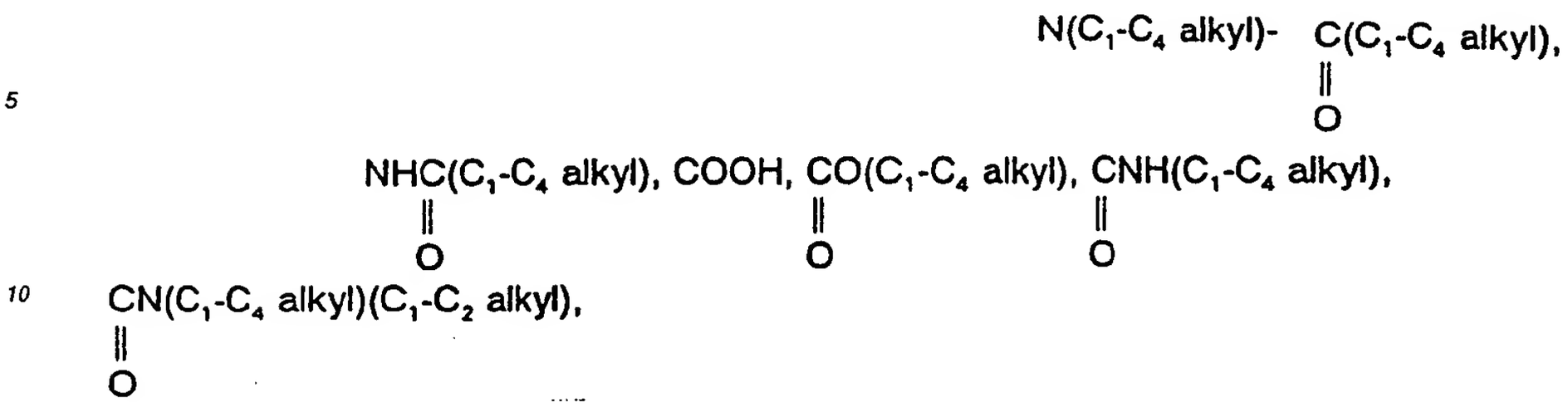
CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl),
‖ ‖
O O

SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4-alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy,

O-C -(C_1-C_6 alkyl),
‖
O

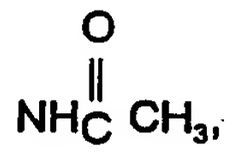
O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl),



SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

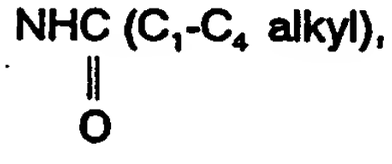
NR_1R_2 or $CR_1R_2R_{11}$ may form a 4-to 8-membered ring optionally containing one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_7 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino,

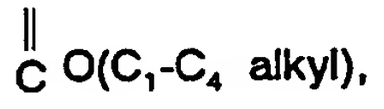


fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl) (C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido,



NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl),



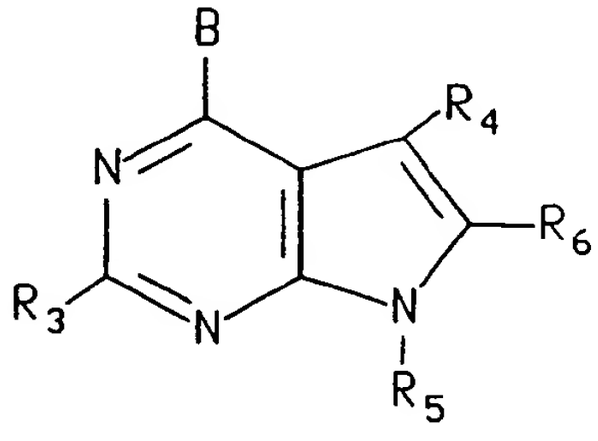
C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, pip r-azinyl, piperidinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1\text{-}C_2$ alkyl), cyano, or $CO(C_1\text{-}C_2$ aklyl); and
R_{12} is hydrogen or $C_1\text{-}C_4$ alkyl;

(a) A is not straight chain $C_1\text{-}C_{12}$ alkyl;
(b) R_5 is not a sugar group;
(c) when R_3 and R_4 are hydrogen and R_5 is chlorophenyl, then A is not $NH\text{-}CH(CH_3)\text{-}(CH_2)_3\text{-}N(C_2H_5)_2$;
(d) when R_3 and R_4 are hydrogen and A is NR_1R_2 wherein R_1 is $C_3\text{-}C_7$ cycloalkyl, and R_2 is $C_2\text{-}C_6$ alkenyl, phenyl-($C_1\text{-}C_6$ alkylene) or hetero-($C_1\text{-}C_6$ alkylene) wherein the hetero radical is furyl, thienyl or pyridinyl, and wherein said phenyl may be substituted by fluoro, chloro, bromo or iodo, then R_5 is not tetrahydrofuranyl or tetrahydropyranyl;
(e) when R_3 is methoxy, methylthio, or methylsulfonyl, R_4 is hydrogen, and R_5 is tetrahydrofuranyl or tetrahydropyranyl, then A is not $NH(C_1\text{-}C_2$alkyl), morpholinyl, hydrazino, or $NHC_2H_4C_6H_5$ which may be substituted by one methyl or two methoxy;
(f) when R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, hydrazino, chloro, bromo, SH, or S ($C_1\text{-}C_4$ alkyl), R_4 is hydrogen and R_5 is $C_3\text{-}C_8$ cycloalkyl, then A is not hydrazino, $NH(C_1\text{-}C_2$ alkyl) or $N(C_1\text{-}C_6$ alkyl) ($C_1\text{-}C_{12}$ alkyl);
(g) when R_3 and R_4 are hydrogen and A is $NH(CH_2)_m$ COOH wherein m is 1-12, then R_5 is not phenyl substituted by one of fluoro, chloro, bromo or iodo;
(h) when R_3 is hydrogen, hydroxy, methylthio, chloro or NHbenzyl, R_4 is hydrogen, and R_6 is chlorophenyl or bromophenyl, then A is not $NH(C_1\text{-}C_{12}$ alkyl), NHallyl, or $N(C_1\text{-}C_6$ alkyl) ($C_1\text{-}C_{12}$ alkyl), wherein said $C_1\text{-}C_{12}$ alkyl may be substituted by NC_2H_5, or NH benzyl which may be substituted by one or two bromo, chloro, fluoro, NC_2H_5 phenyl or morpholinopropyl;
(i) when R_3 and R_4 are hydrogen and R_5 is nitrophenyl, then A is not NHR_2 wherein R_2 is $C_1\text{-}C_{12}$ alkyl which may be substituted by two hydroxy, or R_2 is phenyl or benzyl;
(j) when R_3 is chloro or $O(C_1\text{-}C_6$ alkyl), R_4 is hydrogen, and A is NR_1R_2 wherein R_1 and R_2 are indep ndently hydrogen or $C_1\text{-}C_6$ alkyl, then R_5 is not chlorophenyl; and
(k) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxy-ribofuranosyl; or

(D)



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or $C_1\text{-}C_6$ alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1\text{-}C_8$ alkoxy,

O-C -($C_1\text{-}C_6$ alkyl), O-C NH($C_1\text{-}C_4$ alkyl), O-C -N($C_1\text{-}C_4$ alkyl) ($C_1\text{-}C_2$ alkyl),
‖ ‖ ‖
O O O

amino, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_2$ alkyl)$(C_1\text{-}C_4$ alkyl), $S(C_1\text{-}C_6$ alkyl),

$N(C_1\text{-}C_4$alkyl)C ($C_1\text{-}C_4$ alkyl), NHC ($C_1\text{-}C_4$ alkyl), COOH, C O($C_1\text{-}C_4$ alkyl), C NH($C_1\text{-}C_4$ alkyl),
‖ ‖ ‖ ‖
O O O O

C N($C_1\text{-}C_4$ alkyl)($C_1\text{-}C_2$ alkyl),
‖
O

SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and said $C_1\text{-}C_6$ alkyl may contain one or two double or triple bonds;

R_2 is $C_1\text{-}C_{12}$ alkyl, aryl or ($C_1\text{-}C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, tricolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1\text{-}C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or $C_1\text{-}C_4$ alkyl, or one of hydroxy, bromo, iodo, $C_1\text{-}C_6$ alkoxy,

O-C -($C_1\text{-}C_6$ alkyl), O-C -N($C_1\text{-}C_4$ alkyl)($C_1\text{-}C_2$ alkyl),
‖ ‖
O O

$S(C_1\text{-}C_6$ alkyl), NH_2, $NH(C_1\text{-}C_2$ alkyl), $N(C_1\text{-}C_2$ alkyl) ($C_1\text{-}C_4$ alkyl),

N($C_1\text{-}C_4$ alkyl)-C ($C_1\text{-}C_4$ alkyl), NHC ($C_1\text{-}C_4$ alkyl),
‖ ‖
O O

COOH, C O($C_1\text{-}C_4$ alkyl), C NH($C_1\text{-}C_4$ alkyl), C N($C_1\text{-}C_4$ alkyl)($C_1\text{-}C_2$ alkyl),
‖ ‖ ‖
O O O

SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and wherein said $C_1\text{-}C_{12}$ alkyl or $C_1\text{-}C_{10}$ alkylene may contain one to three double or triple bonds; or

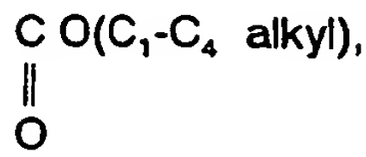
NR_1R_2 or $CR_1R_2R_{11}$, may form a saturated 3- to 8-membered ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl;

R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1\text{-}C_6$ alkyl), $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SH, $S(C_1\text{-}C_4$ alkyl), $SO(C_1\text{-}C_4$ alkyl), or $SO_2(C_1\text{-}C_4$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents R_6 independently selected from the group consisting of hydroxy, $C_1\text{-}C_3$ alkoxy, fluoro, chloro or $C_1\text{-}C_3$ thioalkyl;

R_4 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_2$ alkyl), $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido,

NHC ($C_1\text{-}C_4$ alkyl),
‖
O

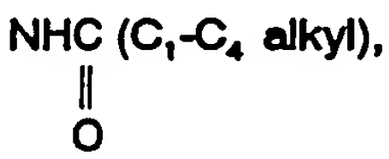
$NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl),



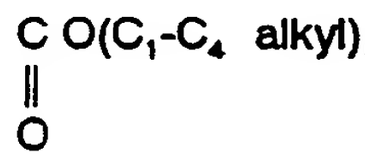
$C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4)(C_1\text{-}C_2$ alkyl), $COO(C_1\text{-}C_4$ alkyl), $CO(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SO_2NH_2, $NHSO_2(C_1\text{-}C_4$ alkyl), $S(C_1\text{-}C_6$ alkyl), $SO_2(C_1\text{-}C_6$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may be substituted by one or two of fluoro, chloro, hydroxy, $C_1\text{-}C_4$ alkoxy, amino, methylamino, dimethylamino or acetyl wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

R_6 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, formyl, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl$)(C_1\text{-}C_2$ alkyl), $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido,



$NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl$)(C_1\text{-}C_2$ alkyl),



$C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1\text{-}C_2$ alkyl), cyano, or $CO(C_1\text{-}C_2$ alkyl); and

R_{12} is hydrogen or $C_1\text{-}C_4$ alkyl; with the proviso that (1) B is not straight chain $C_1\text{-}C_{12}$ alkyl, (2) when R_5 is unsubstituted cycloakyl, R_3 and R_4 are hydrogen, and R_6 is hydrogen or methyl, then B is not NHR_2 wherein R_2 is benzyl or thienylmethyl, and (3) when R_5 is p-bromophenyl, and R_3, R_4 and R_6 are methyl, then B not methylamino or hydroxyethylamino;

for the manufacture of a medicament for the treatment of panic, phobias including agoraphobia, social phobia, and simple phobia, obsessive-compulsive disorder, post-traumatic stress disorder, single episode depression, recurrent depression, dysthymia, bipolar disorders, cyclothymia, mood disorders, postpartum depressi n, child abuse induced depression, sleep disorders, stress induced pain perception including fibromyalgia, fibromyalgic sleep disorders, rheumatoid arthritis, osteroarthritis, psoriasis, euthyroid sick syndrome, syndrome of inappropriate antidiarrhetic syndrome hormone (ADH), bulimia nervosa eating disorder, or obesity.

2. The use according to claim 1, wherein said compound is

2-{1-[1-(2,6-dichloro-4-tirfluoromethylphenyl)-5-dimethylamino-3-ethyl-1H-pyrazol-4-ylmethyl]-napthalen-2-yloxy}-ethanol;

enantiomeric [4-(3-methoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyraz l-3-yl]-dimethylaminederivedfrom(+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline;

enantiomeric [2-(2,6-dichloro-4-trifluoromethylphenyl)-4-(3-ethoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-5- thyl-2H-pyrazol-3-yl]-dimethylamine derived from (+)-3-hydr xymethyl-1,2,3,4-tetrahydroisoquinoline;

[2-(2,6-dichloro-4-trifluoromethylphenyl)-5-ethyl-4-(7-methoxyquinolin-8-ylmethyl) 2H-pyrazol-3-yl]-dimeth-

ylamine;

[2-(2,6-dichloro-4-trifluoromethylphenyl)-4-)2-ethoxy-napthalen-1-ylmethyl)-5-ethyl-2H-pyrazol-3-yl]-dimethylamine;

[4-(2-ethoxynapthalen-1-ylmethyl)-5-ethyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine;

[4-(7-methoxyquinolin-8-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine;

2-{1-[5-dimethlamino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-ylmethyl]-napthalen-2-yloxy}-ethanol;

enantiomeric [2-(2,6-dichloro-4-trifluoromethlphenyl)-5-ethyl-4-(3-methoxymethyl-3,4-dihydro-1H-isoquinolin-2-ylmethyl)-2H-pyrazol-3-yl]-dimethylamine derived from (+)-3-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline; and

[4-(2-cyclopropylmethoxynapthalen-1-ylmethyl)-5-methylsulfanyl-2-(2,4,6-trichlorophenyl)-2H-pyrazol-3-yl]-dimethylamine.

3. The use according to claim 1, wherein said compound is

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dimethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-bis-trifluoromethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone,

[5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone, or

[5-amino-1-(4-bromo-2,6-dimethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dibromophenyl)m th-anone.

4. The use according to claim 1, wherein said compound is

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dimethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyll-1H-pyrazol-4-yl]-(2,5-bis-trifluoromethylphenyl)methanone,

[5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone,

[5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazol-4-yl]-(5-isopropyl-2-methylphenyl)methanone, or

[5-amino-1-(4-bromo-2,6-dimethylphenyl)-3-methylsulfanyl-1H-pyrazol-4-yl]-(2,5-dibromophenyl)methanone.

5. The use according to claim 1 wherein said compound is

3-{(4-methylbenzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-chloro-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine; or

4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylph nyl)-1H-pyrazolo[3,4-d]pyrimidine.

6. The use according to claim 1 wher in said compound is

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethylpropyl)amine; or
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 20 1475

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X D	WO-A-94 13644 (PFIZER INC) 23 June 1994 * claims 1-19,21 * & PCT Application US93/10716	1,2	A61K31/415 A61K31/47 A61K31/505 C07D231/44 C07D231/38 C07D231/52 C07D401/06 C07D405/06 C07D231/18 C07D403/10 C07D409/10 C07D487/04 C07D207/34
A,D	US-A-5 063 245 (M.E. ABREU ET AL) * column 5, line 1 - line 20; claims *	1	
P,X	WO-A-94 13643 (PFIZER INC) 23 June 1994 * claims *	1,3,4	
A	J. MED. CHEM., vol. 27, no. 11, 1984 pages 1396-1400, D.E. BUTLER ET AL * table I, compound 33 *	1,3,4	
A	ARCH. PHARM. (WEINHEIM, GER.), vol. 316, no. 7, 1983 pages 608-616, H. BIERE ET AL * scheme 2 and tables 1-2, compound 3f *	1	
A	DE-A-30 25 579 (LABORATOIRE ROGER BELLON SA) * claims 1, 2, 4, 5, 7; page 10, lines 3-9; table I, examples 13-17 *	1	
P,X D	WO-A-94 13677 (PFIZER INC) * claims * & PCT Application US93/11333	1,5	
A	EP-A-0 287 907 (BOEHRINGER MANNHEIM GMBH) * claims 1,3,4; examples 5,6 *	1	

-/--

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	27 October 1995	Van Amsterdam, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 20 1475

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	INDIAN J. CHEM., SECT. B, vol. 26B, no. 3, 1987 pages 284-286, A. HASAN ET AL * page 285, table 1, compounds 6-12, 14-20, 22-28 * ---	1	
A	INDIAN J. CHEM., SECT. B, vol. 26B, no. 10, 1987 pages 963-967, K. DEO ET AL * page 965, table 1, compounds 5-9, 11, 12, 14-18, 20-24 * ---	1	
A	J. MED. PHARM. CHEM., vol. 5, no. 1, 1962 pages 588-607, E.Y. SUTCLIFFE ET AL * table VII, page 601, entries 4-6, and page 602, entries 2-3 * ---	1	
A	US-A-4 139 705 (J.E. DUNBAR ET AL) * column 1, line 1 - line 55; example 2 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	DE-A-24 30 454 (DR. KARL THOMAE GMBH) * page 7, line 15 - line 25; claims 1,7; examples 27,31 * ---	1	
A	US-A-3 551 428 (J. DRUEY ET AL) * column 2, line 47 - column 3, line 20; examples 13,14,16,17 * ---	1	
P,X D	WO-A-94 13676 (PFIZER INC) * claims 1-11 * & PCT Application US93/10715 ---	1,6	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	27 October 1995	Van Amsterdam, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 20 1475

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	DE-A-31 45 287 (TROPONWERKE GMBH & CO KG) * claims 1,2,4-10; examples 6,8,9 *	1	
A	ANNU. REP.MED. CHEM., vol. 25, 1990 pages 215-224, E.B. DE SOUZA * the whole document *	1	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	27 October 1995	Van Amsterdam, L

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)